REMARKS

Claims 1-22 and 42-63 are pending, with 1, 2, 21, 22, 44, 48, 51, 55, 58 and 61 being the independent claims.

Claims 1, 2, 17, 21, 22, 42 and 43, insofar as the claims are drawn to the elected species of invention, are currently under prosecution. Claims 4-16, 18-20 and 44-63 were withdrawn from consideration as being drawn to a non-elected invention or species of invention.

New claims 84-90 are added.

The Examiner has rejected claims 1, 2, 17, 21, 22, 42 and 43. (2/16/05 Office Action, hereinafter "Office Action")

Elections/Restrictions

As discussed in the Applicant's Amendment filed November 12, 2004 (hereinafter, "11/12/04 Amendment") at page 17, and in the Office Action in §5, process claims that depend from or otherwise include all the limitations of the patentable product will be entered as a matter of right if the amendment is presented prior to final rejection or allowance, whichever is earlier. The Applicant requests the opportunity to rejoin the withdrawn process claims 44-63, amended to include the relevant limitations of the pending product claims, in accordance with the provisions of MPEP §821.04, should the product claims be allowed.

In the 11/12/04 Amendment, the Applicant also affirmed a provisional election to the species of antibody comprising SEQ ID NOs: 45, 155, 157, 22 and 77 that was made during a telephone call with the Examiner on April 19, 2004. The Applicant requests that should the claims currently under consideration be found allowable as they pertain to the elected species, the claims to the non-elected inventions that are linked to the elected invention by allowed linking claims also be examined, in accordance with MPEP § 809.04.

The Applicant is grateful for the opportunity that was provided by the Examiner to discuss the written description and enablement issues of record in the telephonic interview held on June 16, 2005. In the interview, the Examiner indicated that withdrawn process claims 44, 45, 58 and 59, drawn to methods of targeting and detecting angiogenic vasculature, would be enabled. He also

indicated that if the written description and enablement rejections of the pending claims were overcome, he would proceed to examine the next species of the invention. In the interview and summary, the Examiner agreed to carefully consider the amendments discussed, stating that "[if] the written description issue, in particular, is not satisfactorily obviated by the amendment," he agreed to telephone Applicant's representative to discuss possible remedies. (Interview Summary, 6/20/05) Therefore, with regard to the withdrawn method claims and the nonelected species claims, when the Examiner has indicated the allowability of the product claims, the Applicant will submit a supplemental response in which with the previously withdrawn claims have been amended to incorporate the limitations of the allowed product claims.

IDS

The Applicant thanks the Examiner for consideration of the information disclosure statement filed 11/12/04.

Grounds of Objection and Rejection Withdrawn

The Applicant thanks the Examiner for his withdrawal of the objections made and the provisional obviousness-type double patenting rejection set forth in the 5/11/04 Office Action. With regard to the provisional obviousness-type double patenting rejection over U.S. 09/478,977, the Applicant believes, and respectfully states, that the rejection should have been withdrawn for the reasons set forth on pages 26-29 of the Applicant's Amendment and Response of 11/12/04, rather than the reasons, with which the Applicant disagrees, provided by the Examiner in § 7 of the 2/16/05 Office Action.

Claim Rejections under 35 U.S.C. § 112 ¶ 1 – Written Description

The Examiner has maintained the rejection of claims 1, 2, 17, 21, and 22, and claims 42 and 43, insofar as the claims are drawn to the antibody of any of claims 1, 2, 17, 21 and 22, under 35 U.S.C. § 112 ¶ 1 as "containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention." (Office Action, § 8, pp. 4-5, and

5/11/04 Office Action § 17, p. 7) This rejection was originally set forth in § 17 of the 5/11/04 Office Action, wherein the Examiner wrote that "[t]he specification does not describe with any degree of particularity a single member of the genus of 'cryptic collagen epitopes' to which the members of the claimed genus of antibodies must bind, such that the specification might reasonably convey to the skilled artisan that Applicant had possession of the claimed invention at the time the application was filed."

Although the rejected claims defined the invention in terms of a combination of functional and structural characteristics, the Examiner's rejection stated that given the definition of "a cryptic collagen epitope," in the specification, "one could not immediately recognize or distinguish members of the genus of cryptic collagen epitopes to which the members of the claimed genus of antibodies must bind." (*Id.*) Without any evidence or support, the Examiner argued that "it is expected that denatured collagen is actually structurally heterogenous, such that not every molecule of any given preparation of denatured collagen is expected to display the epitope to which the claimed antibodies bind." (Office Action, page 7) Further, the Examiner provides as evidence in the art that denatured proteins are heterogeneous in structure, "autoantibodies to produced in patients with certain autoimmune syndromes are heterogeneous in their epitope specificities, recognizing both conformational and linear determinants." (*Id.*)

The Applicant respectfully points out that heterogeneity among antibodies raised to an antigen is not necessarily evidence of a "structurally heterogeneous" antigen. Rather, as one of skill in the art would expect, there is heterogeneity among antibodies raised to any large protein, because many if not most proteins display multiple epitopes regardless of their state of denaturation.

Nonetheless, even if the structure of the antigen is not described to the Examiner's satisfaction, the Applicant submits that the claims still satisfy the written description requirement. The written description requirement can be met by disclosure of a "sufficiently known" structure in correlation with a functional characteristic, as described in *Enzo Biochem v. Gen-Probe, Inc.*:

> In its Guidelines, the PTO has determined that the written description requirement can be met by "show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics

> ... *i.e.*, complete or partial structure, other physical and/or chemical properties, *functional characteristics when coupled with a known or disclosed correlation between function and structure*, or some combination of such characteristics."

(Quoting from *Guidelines*, 66 Fed. Reg. at 1106) (*Enzo Biochem v. Gen-Probe, Inc.*, 323 F.3d 956, 963 (Fed. Cir. 2002).

In fact, the functional characteristic disclosed in the claims of the *Enzo* patent was preferential binding for one substrate over another:

> "under the [USPTO Application of Written Description] Guidelines, the written description requirement would be met for all of the claims of the '659 patent if the functional characteristic of preferential binding to N. gonorrhoeae over N. meningitidis were coupled with a disclosed correlation between that function and a structure that is sufficiently known or disclosed. We are persuaded by the Guidelines on this point and adopt the PTO's applicable standard for determining compliance with the written description requirement."

(*Id.*) The present application claims antibodies based on a combination of both functional and structural characteristics. The amendments to the claims add no new matter. Support for the amendment adding, "has at least a two-fold higher binding activity for denatured collagen over native collagen," is found in the published application at, e.g., [0036] in Figures 8, 9 and 10, and in the descriptions of the figures at [0016], [0017], and [0018].

Claim 1 is drawn to antibodies having certain protein sequences coupled with a higher relative binding activity for denatured than native collagen. The structure of antibody molecules is well-known to one of skill in the art. It is well-known that antibodies have structurally conserved framework regions that are attached to complementarity-determining regions (CDRs) which vary to allow the antibody to specifically bind to its cryptic collagen epitope. The amino acid sequences of

the CDRs of the claimed antibodies are provided in the patent specification. The claims allow amino acid sequence changes within the CDRs as long as the functional requirements of the claims are met. The current claims and specification specify the structure of the claimed antibodies on the amino acid sequence level, thus providing more than sufficient structural information to satisfy the written description requirement. In addition to this all-but-complete structural information, the specification provides functional characteristics of the claimed antibodies - preferential binding to denatured collagen - removing any doubt that the written description requirement is satisfied.

For example, claim 1, as currently amended, reads:

> 1. A grafted antibody, or functional fragment thereof, comprising the following complementarity determining regions (CDRs): SEQ ID NO:26; SEQ ID NO:28; SEQ ID NO:30; SEQ ID NO:20; SEQ ID NO:22; and SEQ ID NO:24; wherein at least one of said CDRs has at least one amino acid substitution, and wherein said grafted antibody or functional fragment thereof has at least a two-fold higher binding activity for denatured collagen over native collagen.

The disclosed correlation, of the higher relative binding activity for denatured than native collagen with the specified CDR amino acid sequences, provides more than sufficient written description for the claims under 35 U.S.C. § 112 ¶ 1.

According to the Examiner, an epitope of a denatured collagen molecule is not well characterized, and therefore does not meet the written description requirement in the manner indicated by *Noelle v. Lederman*, 355 F.3d 1343, 69 USPQ2d 1508 (Fed. Cir. 2004). (Office Action, p. 5) The relevance of *Noelle*, a case involving claims to antibodies, is the Court's finding that the structure of claimed antibodies does not have to be stated at all. According to the Court, "[i]f Noelle had sufficiently described the human form of CD40CR antigen, he could have claimed its antibody by simply stating its binding affinity for the 'fully characterized' antigen." (*Id.*, at 1349) This case thus builds on the Court's findings in Enzo.

In the interview held on 6/16/05, the Examiner said that he would carefully consider a response filed with specific claim amendments, proposed in the interview by the Applicant, to overcome the rejections for lack of written description. The amendments as discussed in the interview are incorporated in the claim set presented herein.

For the reasons set forth above, Applicant respectfully requests that the rejections of claims 1, 2, 17, 21, 22, 42 and 43 under 35 U.S.C. § 112, ¶ 1 for lack of written description be withdrawn.

Claim Rejections under 35 U.S.C. § 112 ¶ 1 – Enablement

The Examiner has rejected claims 1, 2, 21 and 22, and claims 42 and 43, insofar as the claims are drawn to the antibody of any of claims 1, 2, 21 and 22, under 35 U.S.C. § 112, ¶ 1 for lack of enablement. According to the Examiner, "It would not be expected, for example, that combining any of the variants of CDR1 of monoclonal antibody HUIV26 and any of the variants of CDR2 or CDR3 will always produce a functional antibody that binds the denatured collagen. While not every combination of the disclosed light chain CDRs or heavy chain CDRs is expected to produce a functional antibody that binds a cryptic collagen epitope, the claims can embrace some non-working embodiments. However, the claims also encompass antibodies that bind a cryptic collagen epitope comprising only one or two of the disclosed CDRs." (Office Action, § 9, p. 10)

The Examiner has suggested that the claims be rewritten to more particularly claim the subject matter that the Applicant regards as the invention, and has been kind enough to provide an example of a potential amendment to claim 1. The Applicant has made an effort to amend the rejected claims to incorporate the Examiner's suggested language, to the extent that the proposed changes do not conflict with the suggested amendment to the same claims that was set forth by the Examiner in the next section of the Office Action.

For the reasons set forth above, the Applicant believes that the rejection of claims 1, 2, 21, 22, 42 and 43 under 35 U.S.C. § 112, ¶ 1, for lack of enablement as set forth in § 9 of the Office Action have been overcome.

Claim Rejections under 35 U.S.C. § 112 ¶ 2

The Examiner maintained his rejection of claims 1, 42 and 43 under 35 U.S.C. § 112, ¶ 2 as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention and has proposed an amendment to claim 1. (Office Action, §10, p. 11) The Applicant thanks the Examiner for his suggestions in this and the previous sections. Applicant believes that the claims have been amended according to the Examiner's suggestion, and that the rejection under 35 U.S.C. § 112, ¶ 2 has been overcome.

New Claims 84-90

Support for new claims 84-90 can be found throughout the specification, as well as in the original claims, particularly original claims 2 and 17. New claim 84 is drawn to an antibody having CDRs selected from the group of CDR sequences recited in original claim 2, in addition to certain CDRs having subsets of listed sequences (amino acids 6-10) recited in claim 2. New claim 85, which depends from new claim 84, and new claim 86, are drawn to specific species of claim 84.

New claims 87, 88 and 89 specify an antibody heavy chain framework sequence, as described in the specification and drawings. Support for these claims is provided, for example, at paragraphs [0107], [0010], [0011], [0022] and [0024] of the published application. New claim 88 is drawn to an antibody having an amino acid substitution in the specified antibody framework. Support for claim 88 is provided throughout the application, for example, at [0027], [0095], [105], [106], [108], [109], [110], [111], [112], [113], and [114]. New claim 90 is drawn to the same species as was original claim 17, the only difference being that new claim 90 is written in independent form. The new claims add no new matter to the application.

CONCLUSION

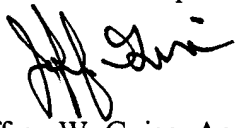
Applicants believe that for the reasons set forth above, the Examiner's rejection of claims 1, 2, 17, 21, 22, 42 and 43 have been overcome. Amendments have been made for the purposes of more clearly stating the claimed subject matter and do not add new matter. The Applicant therefore

respectfully requests allowance of the pending claims. The Examiner is invited to call the undersigned agent at 858.350.2307 if there are any questions.

To the extent necessary, a petition for an extension of time under 37 C.F.R. 1.136 is hereby made. Please charge any shortage in fees due in connection with the filing of this paper, including extension of time fees, to Deposit Account 23-2415 and please credit any excess fees to such deposit account.

Respectfully submitted,

WILSON SONSINI GOODRICH & ROSATI
Professional Corporation



Dated July 18, 2005

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